

We claim:

1. An isolated human monoclonal antibody, or an antigen binding portion thereof, that specifically binds to dendritic cells, wherein the antibody or antigen binding portion thereof has one or more of the following characteristics:
- a) a binding affinity constant to a dendritic cell of at least about  $10^7 \text{ M}^{-1}$ ;
  - b) the ability to opsonize a dendritic cell;
  - c) the ability to internalize after binding to dendritic cells; or
  - d) the ability to activate dendritic cells.
2. The isolated human antibody of claim 1, or an antigen binding portion thereof, having an isotype selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgAsec, IgD, and IgE.
3. The isolated human antibody of claim 1, or an antigen binding portion thereof, which is an IgG1 $\kappa$ .
4. The isolated human antibody of claim 1, or an antigen binding portion thereof, which binds to an antigen present on the cell surface of a dendritic cell.
5. The isolated human antibody of claim 4, or an antigen binding portion thereof, which binds to the macrophage mannose receptor.
6. The isolated human antibody of claim 1, or an antigen binding portion thereof, produced by a hybridoma which includes a B cell obtained from a transgenic non-human animal having a genome comprising a human heavy chain transgene and a human light chain transgene fused to an immortalized cell.
7. The isolated human antibody of claim 1, or an antigen binding portion thereof, produced by a hybridoma selected from the group consisting of A3, A5, A23, A24, A33, B9, B11, B33, B47, C8, C10, C20, C28, C29, C30, C35, E1, E8, E10, E18, E20, E21 and E24.
8. An isolated human monoclonal antibody, or antigen-binding portion thereof, which mediates cytolysis of dendritic cells in the presence of human effector cells.

9. The isolated human antibody of claim 8, or an antigen binding portion thereof, which is capable of mediating cytolysis of dendritic cells by human effector cells at an  $IC_{50}$  of  $1 \times 10^{-7}$  M or less *in vitro*.
10. An isolated human monoclonal antibody, or antigen-binding portion thereof, which inhibits growth of dendritic cells.
11. The isolated human antibody of claim 10, or an antigen binding portion thereof, which is capable of inhibiting growth of dendritic cells at an  $IC_{50}$  of  $1 \times 10^{-7}$  M or less *in vitro*.
12. A hybridoma comprising a B cell obtained from a transgenic non-human animal having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell, wherein the hybridoma produces a detectable amount of a human monoclonal antibody that specifically binds to dendritic cells.
13. The hybridoma of claim 12, wherein the human monoclonal antibody has one or more of the following characteristics:
- a) a binding affinity constant to a dendritic cell of at least about  $10^7$  M<sup>-1</sup>;
  - b) the ability to opsonize a dendritic cell; or
  - c) the ability to inhibit growth or to mediate cytolysis of a dendritic cell in the presence of human effector cells at a concentration of about 10 µg/ml or less *in vitro*.
14. The hybridoma of claim 13, which is selected from the group consisting of A3, A5, A23, A24, A33, B9, B11, B33, B47, C8, C10, C20, C28, C29, C30, C35, E1, E8, E10, E18, E20, E21 and E24.
15. A transgenic non-human animal which expresses a human monoclonal antibody that specifically binds to dendritic cells, wherein the transgenic non-human animal has a genome comprising a human heavy chain transgene and a human light chain transgene.

B) 0551614-050601

16. A method of producing a human monoclonal antibody that specifically binds to dendritic cells, comprising:
- immunizing a transgenic non-human animal having a genome comprising a human heavy chain transgene and a human light chain transgene with dendritic cells, such that antibodies are produced by B cells of the animal;
- isolating B cells of the animal; and
- fusing the B cells with myeloma cells to form immortal, hybridoma cells that secrete human monoclonal antibodies specific for dendritic cells.
17. A bispecific molecule comprising at least one first binding specificity for dendritic cells and a second binding specificity for an Fc receptor.
18. The bispecific molecule of claim 17, wherein the Fc receptor is a human FcγRI or a human Fcα receptor.
19. The bispecific molecule of claim 17, which binds to the Fc receptor at a site which is distinct from the immunoglobulin binding site of the receptor.
20. A composition comprising an isolated human monoclonal antibody or antigen-binding portion thereof of claim 1, and a pharmaceutically acceptable carrier.
21. A composition comprising a combination of two or more isolated human antibodies or antigen-binding portions thereof according to claim 1, wherein each of said antibodies or antigen-binding portions thereof binds to a distinct epitope on a dendritic cell.
22. A method of inhibiting growth of a dendritic cell, comprising contacting a dendritic cell with an isolated human monoclonal antibody, or an antigen binding portion thereof, that specifically binds to dendritic cells, such that the growth of the dendritic cell is inhibited.
23. A method of inducing cytolysis of a dendritic cell, comprising contacting a dendritic cell with an isolated human monoclonal antibody, or an antigen binding portion thereof, that specifically binds to dendritic cells in the presence of an effector cell, such that cytolysis of the dendritic cell occurs.

B  
09551614-0508071

24. A method of treating or preventing a dendritic cell mediated disease, comprising administering to a subject an isolated human monoclonal antibody, or an antigen binding portion thereof, that specifically binds to dendritic cells in an amount effective to treat or prevent the dendritic cell mediated disease.
- 5 25. The method of claim 24, wherein the human monoclonal antibody is conjugated to a binding specificity for a Fc receptor.
- 10 26. The method of claim 24, wherein the human monoclonal antibody is conjugated to a cytotoxin.
27. The method of claim 24, wherein the human monoclonal antibody is conjugated to an immunomodulatory compound.
- 15 28. The method of claim 24, wherein the disease is an autoimmune disease.
29. The method of claim 24, wherein the disease is graft versus host disease.
- 20 30. A method for detecting the presence of a dendritic cell in a sample comprising: contacting the sample, and a control sample, with a human monoclonal antibody, or an antigen binding portion thereof which specifically binds to dendritic cells, under conditions that allow for formation of a complex between the antibody or portion thereof and the dendritic cell; and  
detecting the formation of a complex,  
25 wherein a difference complex formation between the sample compared to the control sample is indicative the presence of a dendritic cell in the sample.
- 30 31. An expression vector comprising a nucleotide sequence encoding a variable and constant region of the heavy and light chains of a human monoclonal antibody, or an antigen binding portion thereof, that specifically binds to dendritic cells, wherein the antibody or antigen binding portion thereof has one or more of the following characteristics:
- 35 a) a binding affinity constant to a dendritic cell of at least about  $10^7 \text{ M}^{-1}$ ;  
b) the ability to opsonize a dendritic cell;  
c) the ability to internalize after binding to dendritic cells; or  
d) the ability to activate dendritic cells.

093101:05001

32. A method for targeting an antigen to a dendritic cell in a subject comprising:  
administering to a subject a human monoclonal antibody, or an antigen binding

5 portion thereof, that specifically binds to dendritic cells, wherein the antibody or antigen binding portion thereof is operably linked to an antigen, such that the antigen is targeted to the dendritic cell.

33. A molecular complex comprising:

10 a) at least one binding specificity for a component on the surface of a dendritic cell; and

b) at least one antigen linked to said binding specificity,

wherein said component mediates internalization of said molecular complex when bound by said binding specificity.

34. The molecular complex of claim 33, wherein one or more of said binding specificities comprises an antibody selected from the group consisting of A3, A5, A23, A24, A33, B9, B11, B33, B47, C8, C10, C20, C28, C29, C30, C35, E1, E8, E10, E18, E20, E21 and E24, and antigen binding fragments thereof.

20 35. The molecular complex of claim 33, wherein said antigen is selected from the group consisting of a tumor antigen, a microbial antigen, a viral antigen, and an autoantigen.

25 36. The molecular complex of claim 33, wherein said antigen is chemically linked to  
said binding specificity.

37. The molecular complex of claim 33, wherein said antigen is recombinantly fused to said binding specificity.

30

38. A method for inducing or enhancing an immune response against an antigen in a subject, comprising administering to said subject a molecular complex, such that the immune response against said antigen in said subject is enhanced or induced, wherein said molecular complex comprises:

5 a) at least one binding specificity for a component on the surface of a dendritic cell; and

b) at least one antigen linked to said binding specificity, wherein said component mediates internalization of said molecular complex when bound by said binding specificity.

10

39. The method of claim 38 wherein the immune response comprises antibodies that bind to the antigen.

40. The method of claim 38 wherein the immune response comprises T cells that bind to the antigen as a component of an MHC-I or MHC-II complex.

15

41. The method of claim 38, wherein the antigen is selected from the group consisting of: a tumor cell antigen, a microbial antigen, and a viral antigen.

42. A method for immunizing a subject, comprising administering to the subject an effective amount of a molecular complex comprising:

20 a) at least one binding specificity for a component on the surface of a dendritic cell; and

b) at least one antigen linked to said binding specificity, wherein said component mediates internalization of said molecular complex when bound by said binding specificity.

25

43. A bispecific molecule comprising at least one first binding specificity for dendritic cells and a second binding specificity for an antigen on a target cell.

30

44. The bispecific molecule of claim 43, wherein the target cell is selected from the group consisting of a tumor cell, a microbial pathogen, a virus and a virus-infected cell.

09651614-050001

45. An isolated human monoclonal antibody, or antigen binding portion thereof, which activates dendritic cells.
46. The isolated human antibody of claim 45, or an antigen binding portion thereof, which induces cytokine release by dendritic cells.
47. The isolated human antibody of claim 45, or an antigen binding portion thereof, which modulates the expression of immunomodulatory receptors on the surface of dendritic cells.
48. The isolated human antibody of claim 45, or an antigen binding portion thereof, wherein the immunomodulatory receptor is selected from the group consisting of: CD80 (B7.1), CD86 (B7.2), CD40, and CD54 (ICAM).
49. A method for targeting a cell to a dendritic cell comprising:  
linking a human monoclonal antibody, or an antigen binding portion thereof, that specifically binds to dendritic cells to the surface of a cell, such that the cell is targeted to a dendritic cell.
50. A method for targeting a cell to a dendritic cell comprising:  
transfecting a cell with a nucleic acid molecule encoding a human monoclonal antibody, or an antigen binding portion thereof, that specifically binds to dendritic cells, such that the cell expresses the antibody, or an antigen binding fragment thereof on the surface of the cell, thereby targeting the cell to a dendritic cell.
51. An isolated human monoclonal antibody, or an antigen binding portion thereof, that specifically binds to dendritic cells, the antibody comprising a variable light chain having the amino acid sequence shown in SEQ ID NO:2 and a variable heavy chain having the amino acid sequence shown in SEQ ID NO:4.
52. An isolated human monoclonal antibody, or an antigen binding portion thereof, that binds to and blocks the human mannose receptor on dendritic cells.
53. A method of preventing binding of a pathogen to the human mannose receptor on dendritic cells comprising contacting the antibody or antigen binding portion thereof of claim 52 with dendritic cells in an amount sufficient to prevent binding of the pathogen to the cells.

0551614.050801

- 77 -

54. The method of claim 53, wherein the pathogen is a virus or a bacterium.
55. An isolated human monoclonal antibody, or an antigen binding portion thereof,  
5 that specifically binds to an antigen having a molecular weight of between 36-40 kD as  
measured by PAGE on human dermal dendritic cells, human epidermal dendritic cells,  
and dendritic cells derived from cynomolgus macaques.

09351614.050801  
108950.47475850